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TITLE: Integrative Physiology of Gulf War Illness: Role of Autonomic Function, Central Neural Processing, and Sleep

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14. ABSTRACT About 25% of Gulf veterans (GVs) report major problems with fatigue, widespread pain, cognition, and unrefreshing sleep – Gulf War Illness (GWI). Despite this high prevalence, current treatments have not proven effective. To advance the state of knowledge in GWI, a symptom based syndrome, future work needs to better understand the pathophysiology of the disease. The major objective of this contract was to prepare a grant proposal to test the following hypotheses: (a) that perturbation in one or more of several physiological systems (Autonomic, Sleep, Central Neural Processing) is responsible for the genesis of symptoms of GWI; (b) that assessing these baseline abnormalities with both an acute laboratory stressor and a chronic exercise resistance training regimen will uncover further abnormalities in one of more of these systems; and (c) that studying multiple systems will allow us to uncover interactions among systems that magnify the effect of any one. Thus, by using an integrative approach to understanding the pathophysiology, we will for the first time be able to understand how impairments in various physiological symptoms may not only interact but may underlie the genesis of symptoms. In addition, we will be able to target novel treatments based on the underlying pathophysiology.					
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Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	6
Reportable Outcomes.....	6
Conclusion.....	6
References.....	7
Appendices.....	7

INTRODUCTION

About 25% of Gulf veterans (GVs) report major problems with fatigue, widespread pain, cognition, and unrefreshing sleep – Gulf War Illness (GWI). Despite this high prevalence, current treatments have not proven effective. To advance the state of knowledge in GWI, a symptom based syndrome, future work needs to better understand the pathophysiology of the disease. The major objective of this contract was to prepare a grant proposal to test the following hypotheses: (a) that perturbation in one or more of several physiological systems (Autonomic, Sleep, Central Neural Processing) is responsible for the genesis of symptoms of GWI; (b) that assessing these baseline abnormalities with both an acute laboratory stressor and a chronic exercise resistance training regimen will uncover further abnormalities in one of more of these systems; and (c) that studying multiple systems will allow us to uncover interactions among systems that magnify the effect of any one. Thus, by using an integrative approach to understanding the pathophysiology, we will for the first time be able to understand how impairments in various physiological symptoms may not only interact but may underlie the genesis of symptoms. In addition, we will be able to target novel treatments based on the underlying pathophysiology.

BODY

This award was completely successful since a full consortium application was submitted June 19th to allow for the development of a complete integrative physiology program to understand the pathophysiology of Gulf War Illness and to develop novel treatments based on the underlying pathophysiology.

Summary of Accomplished Work based on submitted Statement of Work

- 1) Establish consortium planning structure (week 1)
 - a. Developed consortium planning structure consisting of leadership group with PI, co-PI, Team Leads, Statistician, Research Administrator which met weekly throughout grant period to ensure progress on all aspects of development of grant proposal
 - b. Three scientific teams (Autonomic, Sleep, Central Neural Processing) were formed and a Data Management & Statistical Team which met adhoc to complete assigned tasks
- 2) Hire Research Administrator
 - a. A research administrator was hired within the first month and took over administrative tasks including organizing weekly leadership meetings and taking minutes and distributing minutes as well as action items, etc.
- 3) Form Advisory Committee
 - a. Representatives were recruited from the Gulf War Resource Center, Veterans of Foreign Wars, Disabled Veterans of America and NJ Department of Veterans Affairs.
 - b. Monthly teleconferences were conducted to get veteran input on all aspects of proposed project to ensure both the goals and feasibility of the proposed research fit in with veteran priorities
 - c. A face to face meeting took place at the War Related Illness & Injury Study Center in April to go over full grant proposal for input before final version was written
- 4) Form External Grant Review Committee
 - a. Four senior research scientists with experience in Gulf War research were recruited to form a review committee to review the proposal in May before submission in June
 - b. Review committee members provided feedback that further enhanced the scientific quality of the proposal
- 5) Initial Planning Meeting
 - a. To enhance collaboration among all investigators, a mandatory 2 day meeting of all investigators took place at the War Related Illness & Injury Study Center (Coordinating center) in Sept. 2011 to discuss the scientific premise of the proposal.
 - b. During meeting group consensus was achieved on overall scientific aims of proposal and structure of consortium
 - c. Areas of interdisciplinary collaboration were discussed and highlighted.
- 6) First Draft of Scientific Content
 - a. Developed first draft of scientific content based on discussion during initial planning meeting
 - b. Draft was revised with input from leadership team, and veteran advisory group.

- 7) Obtain Statistical Support
 - a. Statistician with extensive experience in large data sets and understanding issue of integrative physiology was recruited
 - b. Statistician provided input on calculating sample size necessary to achieve scientific aims as detailed in first draft of proposal
- 8) Develop Logistics plan
 - a. Facilities and available equipment at each data collection site were determined
 - b. Requirements were developed for what equipment was necessary at each site to be able to complete scientific protocols as proposed
 - c. Based on sample size and scientific protocols, it was determined what FTE equivalents and expertise were necessary to carry out protocol at each site
 - d. Primary data analysis sites were assigned to analyze data obtained at all sites in each specific scientific area
- 9) Recruitment Plan
 - a. Meeting with Veteran Service Organizations representatives on Veteran Advisory Group developed plan for best way to perform outreach to Gulf War Veterans
 - b. Developed plan to meet recruitment goals with input from Veteran Advisory Group to ensure recruitment goals would be met
 - c. Developed alternate plan to enhance recruitment in sites that fail to meet their recruitment goals initially
 - d. Tested ability to reach Gulf War Veterans with online survey that was promoted by Veteran Service Organizations and was able to reach over 800 veterans with 555 screening positive for Gulf War Illness confirming we could meet our recruitment goals
- 10) Intellectual Property Plan
 - a. Developed draft agreement on sharing of intellectual property at coordinating center
 - b. Disseminated to all institutions
- 11) Second Draft of Scientific Content
 - a. Based on program announcement, statistical input, logistic plan developed and recruitment plan, we revised scientific plan to consider what can be effectively accomplished across all sites
 - b. Finalized protocol and scientific content
- 12) Data Management Plan
 - a. Determined how data will be moved between each of the primary sites
 - b. Determined how a data repository can be developed with all data available to all investigators
 - c. Determined how data will be accessed securely
 - d. Developed data quality control plan to ensure that data entered into repository is accurate
- 13) External Review of Scientific Content
 - a. Provided second draft of proposal to both the Veteran Advisory Group and Scientific Review Group for final input
- 14) Final Consortium Proposal
 - a. Revised final proposal based on feedback from advisory and review group
 - b. Obtained letters of support from Veteran Service Organizations and institutions involved
 - c. Finalized all supporting documents
 - d. Submitted full proposal on June 19, 2012
- 15) Institutional Review Board Submission
 - a. Initial draft of protocol was written at coordinating center
 - b. Contacted IRB chairman at each institution to determine if they will enter into a reciprocal agreement between IRB at Coordinating Center
- 16) Institutional Review Board Approval at all sites
 - a. Developed IRB submissions for all sites
 - b. Did not submit since proposal was not funded
- 17) Quality Control Plan
 - a. Developed plan to ensure quality of data at all sites
 - b. Developed theoretical data audit system to ensure quality of data at all sites
 - c. Planned comparison of neuroimagers to ensure imaging from multiple sites are comparable
 - d. All work was left in draft format since proposal was not funded
- 18) Training Plan
 - a. Developed plan for training research assistants from all sites to ensure consistency of data collection

- b. Developed training manual for all sites to ensure training is identical across sites
- c. Developed logistic plan to allow RAs to be trained by each investigator in appropriate data collection
- d. All work was left in draft format since proposal was not funded

KEY RESEARCH ACCOMPLISHMENTS:

- Completed Integrative Physiology Proposal to Understand Pathophysiology of Gulf War Illness and Translation of Those Findings into Novel Treatments
- Worked with American Autonomic Society to developed symposium for 2013 Annual Meeting to highlight Gulf War Illness to increase awareness of Gulf War Illness and attract new researchers to the area

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

- Scientific Proposal to Understand Pathophysiology of Gulf War Illness
- Institutional Review Board draft application of protocol to understand Pathophysiology of Gulf War Illness
- Draft Training Manual for Autonomic, Sleep and Central Neural Processing procedures
- Draft Data management plan to allow sharing of data across VA facilities and institutions involved in consortium
- Accepted Symposium on Gulf War Illness and Chronic Fatigue in Veterans for Autonomic Society Annual Meeting in 2013

CONCLUSION:

The Consortium proposal developed provides the unique opportunity to leverage the experience of both senior and younger GWI researchers with a number of investigators that will enter the field of GWI research. The investigators of these projects have established records in the areas of musculoskeletal pain, fatigue, sleep research, and autonomic function, including exercise and functional neuroimaging studies of GVs with GWI. Dr. Natelson has studied GVs and civilians with fatiguing illness for almost 20 years. This Consortium brings together his experience with that of Dr. Cook who has a funded Merit Review project studying GVs with chronic pain and also brings new researchers into the field of GWI research including Dr. Wylie, a neuroimaging expert in fatigue, Drs Pigeon and Heffner with expertise in sleep in veterans of other eras, Dr. Quigley an expert in

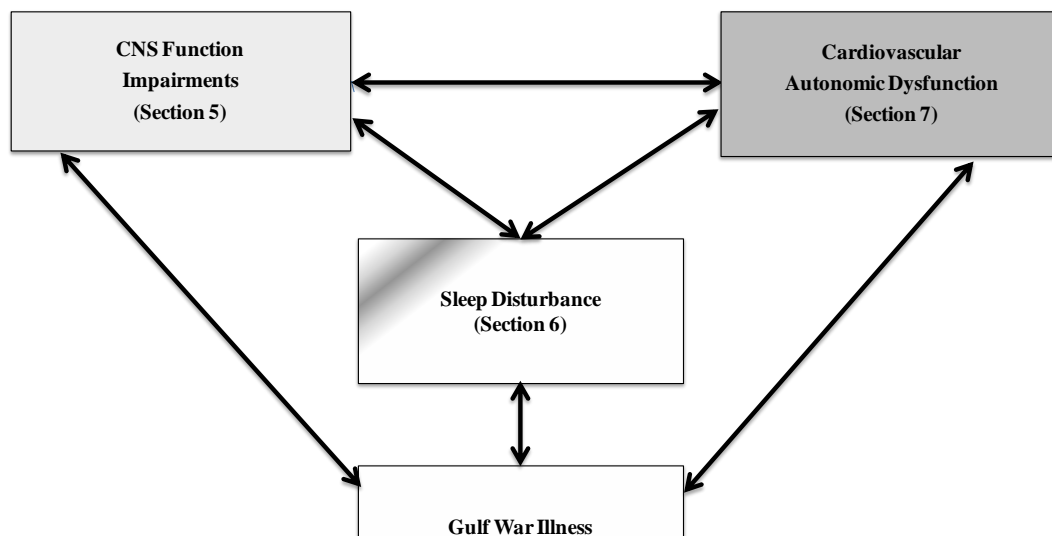


Figure 1. Conceptual diagram of how physiological systems affect symptoms of GWI as well as how deficits in each physiological system may affect other physiological system.

autonomic function in both active duty and veterans of OEF/OIF. Dr. Serrador, the PI, is an established researcher in integrative physiology who will bring his expertise to the area of GWI, while coordinating the integration of the different areas of physiology being studied.

In addition to the specific work proposed, our integrative physiology Consortium provides for pilot funds which will attract researchers studying other systems to work on the GWI problem – thus expanding our knowledge as to the pathophysiology of GWI. Our Consortium is a structure that allows an ever expanding program of research where findings from multiple physiological systems can be translated into novel treatment programs, an area that is desperately needed for veterans with GWI.

REFERENCES: None

APPENDICES: None